REMARKS

Upon entry of the present amendment, claims 45-57, 60-63, 65-69 and 83 will be pending in the above-referenced patent application and are currently under examination. Claims 45 and 63 have been amended. Support for the amendments can be found at page 19, lines 15 to 29. Claims 58-59, 64 and 70-82 have been canceled. Reconsideration of the application is respectfully requested.

The claims are rejected in various combinations under 35 U.S.C. § 112, 1st and 2d paragraphs, as well as an obviousness-type double patenting rejection. Each of these rejections is addressed below in the order set forth by the Examiner.

I. REJECTION UNDER 35 U.S.C. § 112, 1ST PARAGRAPH, ENABLEMENT

Claims 45-57 and 60-63 have been rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection.

Fulfillment of the enablement requirement

The test for enablement is whether the experimentation needed to practice the invention is undue or unreasonable (*Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916)) such that "the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention" (MPEP § 2164.01).

The Examiner is respectfully reminded that routine screening of even large numbers of samples does not constitute undue experimentation under *Wands*. "The test is not merely quantitative, since ***a considerable amount of experimentation is permissible, if it is merely routine***, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (emphasis added).

In *Wands*, the Federal Circuit held that the specification was enabling and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known" *Wands* at 1406. The same is true of the present application. Indeed, the patentee in *Wands* made experimental attempts to identify 143 "high-binding" hybridomas from 10 myeloma-B lymphocyte fusions (of which four fusions completely failed), and then identified only four hybridomas of interest from the 143 "high binders." *Wands* at 1405. The applicant in *Wands* carried out the procedure for making a monoclonal antibody three times and each time successfully produced at least one such antibody. Although the Applicant in *Wands* performed what might be considered as a considerable amount of experimentation, this quantity of experimentation is permissible under the enablement requirement, since the experimentation is merely routine and not undue.

Furthermore, as stated by the MPEP § 2164.02, the presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure. Because only an enabling disclosure is required, Applicant need not describe all actual embodiments. For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient. The present application has certainly complied with this standard.

Finally, the presence of inoperative embodiments in the scope of the claim does not render a claim lacking enablement if only routine experimentation is required to determine which embodiments are operative. MPEP § 2164.08(b).

Only routine experimentation is required to practice the invention set forth in amended claim 45

The Examiner alleges that the compounds of Figure 7 are enabled for the treatment of anxiety but that other compounds within the scope of the claims are not enabled given the alleged breadth of X, Ar^1 and Ar^2. Applicants note that Ar^2 of claim 45 has been presently amended to read "Ar^2 is a 5-6 membered aromatic ring containing 1-3 heteroatoms wherein said heteroatoms are each independently selected from the group consisting of N, O and

S." Accordingly, Ar^2 can only be a subset of the genus heteroaryl, namely a 5 or 6 membered heteroaryl ring with one, two or three of the heteroatoms N, O and S.

In light of the new amendments, the amended claims of the instant application are commensurate with the disclosure and are enabled by the specification. Any experimentation necessary to practice the full scope of amended claim 45 is merely routine.

The specification sets forth a number of simple assays to identify KCNQ channel openers. The assays involve the *in vivo* or *in vitro* treatment of a sample containing a KCNQ channel with a potential KCNQ channel opener and subsequent measurement of the KCNQ potassium channel activity. See specification, page 23, lines 25-29. The activity of the test compound may then be compared with untreated control samples. See specification, page 23, lines 27-29. Such assays can be conducted using high throughput screening methods and large libraries of chemical compounds, which are well known in the art, and systematic screening of potential KCNQ channel openers can be aided by robotic automation. See specification, page 25, lines 21-27. KCNQ potassium channel opening activity may be determined by measuring changes in ion flux through detection of cell or membrane polarization. See specification, page 24, lines 4-6. Cell or membrane polarization is detected by measuring changes in current using standard techniques such as voltage clamps or patch clamps. See specification, page 24, lines 6-10. These assays can be used routinely to determine whether or not a selected compound acts as a KCNQ channel opener.

Other standard assays for measuring ion flux are also disclosed, such as those involving the measurement of potassium or rubidium ions flux by directly detecting the concentration changes of the ions (e.g., radioisotopic labeling). See specification, page 24, lines 23-32. In addition, ion flux may be measured by determining changes in physiological conditions, such as transmitter release (e.g., dopamine), hormone release (e.g., insulin), transcriptional changes to both known and uncharacterized genetic markers (e.g., northern blots), cell volume changes (e.g., in red blood cells), immunoresponses (e.g., T cell activation), changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second

messengers such as Ca^{2+}, or cyclic nucleotides. See specification, page 24, line 30 to page 25, line 8.

The specification further provides an array of methods useful in identifying KCNQ channel openers (page 23, lines 12-18). The specification also sets forth simple assays to test potassium channel openers for their ability of treat anxiety. Again, these assays can be used routinely to identify operable embodiments of the invention. On page 12, line 16 to page 13, line 3, the specification provides a detailed description of assays useful in testing anxiolytic effects:

The standard test in rat to measure anxiolytic effect (Geller conflict procedure) was designed by Geller and Seifter and modified by Pollard and Howard (Geller & Seifter, *Psychopharmacologia* 1:482-492 (1960: Pollard & Howard, *Psychopharmacology* 62:117-121 (1979)). The anxiety-reducing effect of a KCNQ2/3 channel opener was measured using the Geller conflict procedure in rats. Rats are trained to press a lever to receive food pellets during daily 1 hour sessions. The sessions are divided into punished and unpunished phases. During the four, three-minute punished periods, a light signals that each lever press will produce both a pellet and a foot shock (punishment), which reduces lever pressing. The number of punished lever presses on test days (when test compound is administered) is compared to the mean on baseline days. The positive control, chlordiazepoxide, increases punished lever pressing by > 50%. A compound that produces an increase of approximately 40% or greater is generally considered to be of interest as a rapid-onset anxiolytic. A selective KCNQ2/3 channel opener increased punished responding in a dose dependent, statistically significant manner (Figure 6).

Moreover, as evidence of the routine nature of these disclosed assays, Applicants note the declaration of Dr. Douglas Krafte, filed with Applicants' response of December 22, 2005, who states that the Geller assay is an art accepted model for testing anxiety compounds. Dr. Krafte further states that one skilled in the art need only practice routine assays generally known in the art and explicitly disclosed in the specification to practice the invention as set forth in amended claim 45. Moreover, Dr. Krafte declares that he is not aware of any reasoning or evidence as to why one skilled in the art would doubt the usefulness of the disclosed assays.

Thus, Applicants assert that one skilled in the art, using the teachings in the specification and methods generally known in the art, would be able to determine the ability of KCNQ channel openers of amended claim 45 to treat anxiety in a subject. Absent some reasoning or evidence to doubt the usefulness of the methods disclosed in the specification, Applicants submit that one skilled in the art would recognize that Applicants fully enabled a method of identifying a KCNQ potassium channel opener useful in treating anxiety.

A working example of in vivo treatment of anxiety

The specification also provides a working example of the claimed invention in which a KCNQ channel opener is administered in accordance with the protocol of the Geller conflict model. See Example 6. As pointed out by Dr. Krafte in his expert declaration, filed with Applicants' response of December 22, 2005, this example demonstrates that the invention as claimed works for its intended purpose. The Examiner has presented no evidence or reasoning as to why one skilled in the art would doubt the validity of this experiment. Moreover, the Examiner has presented no evidence or reasoning as to why one skilled in the art, after examining this experiment, would conclude that a KCNQ channel opener would ***not*** work as intended in amended claims 45-57.

Therefore, Applicants respectfully submit that one skilled in the art would recognize that Applicants have enabled a method of reducing anxiety using a compound of amended claim 45 that increases ion flow through a KCNQ potassium channel as claimed. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

II. REJECTION UNDER 35 U.S.C. § 112, 1ST PARAGRAPH, WRITTEN DESCRIPTION

Claims 45-57 and 60-63 have been rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

The test for written description is whether the specification describes "the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor

had possession of the claimed invention." See, *e.g.*, *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116-17. "The subject matter of the claim need not be described literally (i.e., using the same terms or in *haec verba*) in order for the disclosure to satisfy the description requirement." (MPEP §§ 2163, 2163.02).

The Examiner alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. As noted above, Ar^2 of claim 45 has been amended to read "Ar^2 is a 5-6 membered aromatic ring containing 1-3 heteroatoms wherein said heteroatoms are each independently selected from the group consisting of N, O and S." Accordingly, Ar^2 can only be a subset of the genus heteroaryl, namely a 5 or 6 membered heteroaryl ring with one, two or three of the heteroatoms N, O and S.

The amendments to Ar^2 of claim 45 find adequate written description support in the specification as filed. Specifically, the structures in Figure 7 provide support for heteroaryls, specifically N-containing heteroaryls. In addition, the definition for heteroaryl on page 19, lines 17 to 29 provide adequate support. The definition of heteroaryl in the specification provides that heteroaryl "refers to aryl groups (or rings) that contain from *zero to four heteroatoms selected from N, O, and S*, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized." (emphasis added) Provided with the definition of heteroaryl in the specification and the structures in Figure 7, there exists sufficient written description for amended claim 45. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

III. REJECTION UNDER 35 U.S.C. § 112, 2D PARAGRAPH

Claims 45-57 and 60-63 have been rejected under 35 USC § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants respectfully traverse the rejection in view of the comments below.

The test for indefiniteness is "whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity" (MPEP § 2173.02). This analysis does not occur in a vacuum, but rather in view of the following factors: (1) the content of the particular application disclosure; (2) the teachings of the prior art; and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. In addition, "the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope" (MPEP § 2173.02).

The Examiner alleges that the terms aryl and heteroaryl are indefinite, in view of an absence of the size of the rings, the number and nature of the heteroatoms in the heteroaryl ring, as well as the connectivity of the rings. Applicants note that Ar^2 of claim 45 has been amended to read "Ar^2 is a 5-6 membered aromatic ring containing 1-3 heteroatoms wherein said heteroatoms are each independently selected from the group consisting of N, O and S." This description specifically provides the ring size as well as the nature and number of the heteroatoms included in the ring.

Furthermore, page 19, lines 22-27 provide examples of compounds that are covered by the definition of aryl and heteroaryl. A review of these examples reveals that the size of the aryl ring can be from 5 (thienyl, furanyl) to at least 12 members (biphenyl). In addition, there can be up to several heteroatoms present, such as N, O and S in a variety of combinations (isoxazolyl, thiazolyl, pyridyl, quinoxalinyl). Furthermore, the connectivity of the ring systems can be fused (indolyl, naphthyl), or linked (biphenyl). In view of examples of fused and linked connections, one of skill in the art would appreciate that other connections, like spiro-connected or bridged groups are within the scope of the invention.

While the description of aryl and heteroaryl on pages 19-20 is adequate to particularly point out and distinctly claim the compounds of the present invention, Applicants have amended Ar^2 to further define the compounds of the present invention in an effort to advance prosecution. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

IV. OBVIOUSNESS-TYPE DOUBLE PATENTING

Applicants respectfully note that upon allowance of the claims, a terminal disclaimer will be filed in view of any outstanding obviousness-type double patenting rejections.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

Frank J. Mycroft
Reg. No. 46,946

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300

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